

Brain Access of Monoclonal Antibodies as Imaged and Quantified by ^{89}Zr -Antibody PET: Perspectives for Treatment of Brain Diseases

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In the search for effective therapies against central nervous system (CNS) diseases, it is questioned whether sufficient intralesional drug concentrations can be reached on systemic administration. This is especially true for biologicals such as monoclonal antibodies (mAbs), which are relatively large. Few patient data are available on the passage of mAbs over an intact blood–brain barrier (BBB), because reliable, time-effective, and noninvasive methods to quantify drug concentration in the brain are lacking. In this issue of *The Journal of Nuclear Medicine*, Lesniak et al. use PET imaging of the mAb bevacizumab labeled with the long-lived positron emitter ^{89}Zr (half-life, 78 h) to quantify uptake in different brain regions in mice for extended periods of days (1). With this study, they provide avenues to overcome 2 major obstacles in the development of effective treatment strategies for CNS diseases: adequate drug concentrations by chemical opening of the BBB, and efficacious drug monitoring by in vivo imaging and quantification of brain uptake over a prolonged time.

The prospects for patients with glioblastoma, for example, have not improved for decades, with less than 5% of patients surviving 5 y after diagnosis (2). This brief survival is in contrast to the spectacularly increased survival of patients with specific hematologic and solid malignancies outside the brain. Historically, lack of success from chemotherapeutic strategies in brain tumors was presumed to be due to chemoresistance of cancer cells, resulting in studies investigating high-dose or multidrug regimens, as well as targeted therapies such as mAbs. After lack of response in patients, the reigning paradigm of intrinsic tumor chemoresistance shifted to a supposed delivery problem over a blood–brain and blood–brain-tumor barrier. Noninvasive methods to quantify drug concentration in brain and tumor, however, are lacking, and theories regarding BBB integrity are based mainly on MRI studies using contrast agents. Contrast enhancement is assumed to reflect extravasation through a

locally disrupted BBB. BBB disintegration is seen in many CNS disorders such as encephalopathy, multiple sclerosis, Alzheimer disease, Parkinson disease, seizures, stroke, and trauma (3). In brain tumors, especially in lower-grade diffuse gliomas with extensive infiltration in the normal brain, the BBB is probably largely intact, as is reflected by limited contrast enhancement on gadolinium administration. Regions of contrast enhancement, on the other hand, are associated with formation of disordered and highly permeable tumor neovasculature indicating higher malignancy and consequently shorter survival. Since contrast enhancement is only an indirect proof of possible drug penetration through the BBB, direct methods to quantify drug concentrations in brain are urgently needed (4).

In normal, nondiseased brain, the BBB meticulously regulates inter- and paracellular transport of substances via passive diffusion and active transport mechanisms. Transport over the BBB depends on both the physicochemical properties of the drug itself (e.g., lipophilicity, molecular weight, and charge) and its affinity for in- and efflux transporters and receptors (e.g., adenosine triphosphate-binding cassette transporters). El-Khouly et al. recently developed a theoretic model including all these parameters for a long list of commonly used anticancer drugs to review their likeliness of passage over an intact BBB (5). They predicted that only few drugs, 8 of 51 (15%), actually penetrate the BBB on systemic administration, which may explain the lack of efficacy in clinical trials thus far. Yet again, this model is only a theoretic one, and direct methods to quantify actual concentration in brain over time are urgently needed.

To overcome the presumed drug delivery obstacle in the brain, many treatment strategies for CNS diseases are directed at disrupting, passing, or bypassing the effective BBB. Disruption has been tried chemically, by drugs that influence passive diffusion (e.g., bradykinin, mannitol, regadenoson, and borneol) or active transport mechanisms (e.g., elacridar), or externally such as by radiotherapy, ultrasound, or microwaves. Passing the BBB has been tried via viral vectors, nanoparticles, liposomes, exosomes, and transporter or receptor ligands. Novel technical approaches such as convection-enhanced delivery are being developed to bypass the BBB. In these studies, small molecular agents were often used, and biologic agents of larger molecular weight, such as mAbs, were very limited.

As for mAb therapy, evidence for a drug delivery problem over an intact BBB is provided by the fact that mAbs are used with increasing success against various solid tumors outside the brain, such as lymphoma, breast cancer, and colorectal cancer, but disappoint for use in brain tumors and other brain diseases. Even more so, in breast cancer patients, tumor response was observed after systemic mAb treatment, whereas their intracranial metastases did not respond.

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Nonetheless, mAbs are broadly explored, not only for cancer but also for other CNS diseases such as Alzheimer, Parkinson, multiple sclerosis, and stroke because of their specificity and high affinity for critical disease targets. Moreover, mAbs can be labeled with radioactive isotopes to allow the study of functional behavior *in vivo*. By labeling mAbs with, for instance, the long-lived radionuclide ^{89}Zr , whole-body biodistribution and selective brain uptake can be visualized and quantified by PET at high sensitivity and resolution over days, rendering this approach superior to other molecular imaging approaches. Nevertheless, a limiting factor of clinical ^{89}Zr -antibody PET (also referred to as ^{89}Zr -immuno-PET) is the radiation burden to patients, which is relevantly reduced by the introduction of high-sensitivity whole-body PET scanners. A recent review summarizes the distinguished advantages and the first 15 clinical trials using ^{89}Zr -antibody-PET (6). One of these studies was the first to apply ^{89}Zr -labeled bevacizumab PET imaging in pediatric patients with diffuse intrinsic pontine glioma (7), demonstrating substantial variability in the level of ^{89}Zr -bevacizumab tumor uptake within the contrast-enhancing MRI areas. This finding indicated the added value of ^{89}Zr -antibody PET in explaining the poor prognosis of these patients by BBB integrity. Additionally, ^{89}Zr -antibody PET showed value in women with HER2-positive metastatic breast cancer (8). Here, an 18-fold higher uptake of trastuzumab was observed in brain metastasis as small as 0.7 mm, and previously undetected by MRI, than in normal brain tissue. This result is in line with growing evidence that brain metastasis could disrupt the BBB once the diameter exceeds 0.5 mm (9). The evidence that mAb delivery to brain metastasis is possible supports the use of trastuzumab therapy. This is an important finding because there is an increase in brain metastasis among women with HER2-positive breast cancer as a consequence of improved systemic therapy. Visualization and quantification of mAb uptake by PET could decrease the risk of experiencing morbidity and mortality as a result of uncontrolled brain metastases, which often occurs at a time when the primary tumor is apparently under control.

Lesniak et al. perform ^{89}Zr -bevacizumab PET imaging in non-tumor-bearing mice using 4 drug delivery strategies: intravenous infusion with intact BBB or with BBB-opening by administering mannitol 15 min beforehand, versus intraarterial infusion with intact BBB or BBB-opening by coadministration of mannitol. Of note, a gradual linear increase in ^{89}Zr -bevacizumab concentrations was observed until at least 24 h after infusion, contrary to the immediate clearance from brain of many nanoparticles or small molecules. Most importantly, the fastest and highest brain uptake was measured from intraarterial administration of bevacizumab in combination with BBB opening. Finally, negligible drug concentrations were measured in the contralateral hemisphere, indicating selective delivery and toxicity.

The results of this study are intriguing; however, a prominent question arises: Why did the authors choose to renew this therapeutic strategy? Intraarterial treatment of brain diseases has been attempted since the 1950s, and the first phase I studies on osmotic opening of the BBB by mannitol date back to 1979 (10,11). These strategies have since not been adopted for patients after lack of success in clinical studies over the next decades. On the one hand, the endovascular treatment approach remains appealing, because it is minimally invasive and has proven to be safe, with a complication rate of 0.30% (12). On the other hand, after intraarterial delivery of chemotherapy, vascular and neurologic toxicity was reported, with visual loss, stroke, and leukoencephalopathy, compared with the same drug dose given systemically, although these toxicities were attributed to the specific drugs that were administered (13).

What do we learn from the study performed by Lesniak et al.? From decades of previous investigations, we learned that intraarterial

delivery of neurotoxic drugs for brain diseases is a promising yet risky treatment approach. Selecting the right drug and right dose are crucial, especially without proven clinical efficacy of intraarterial drug delivery. Currently, there are 4 active open phase I or II clinical studies combining osmotic BBB disruption using mannitol with intraarterial infusion (NCT00303849, NCT02861898, NCT02800486, and NCT01269853), 3 of which use mAbs at a therapeutic dose. None of the trials, however, include actual drug concentration measurements. We learn from Lesniak et al. that similar studies should include actual drug concentration measurements that are feasible with minimally invasive ^{89}Zr -antibody PET. Ideally, all phase I and II clinical trials should be directed primarily at obtaining information on drug distribution to indicate potential toxicity and on actual disease targeting to indicate potential efficacy. Today, newly developed phase 0 pharmacokinetic and pharmacodynamic studies for brain diseases depend largely on invasive procedures at single time points, such as lumbar puncture or brain biopsy. Lesniak et al. show the added value of ^{89}Zr -antibody PET imaging over time as a potential imaging biomarker for drug toxicity and efficacy. This can facilitate better understanding of the earlier lack of success and can prevent potentially toxic, expensive, and useless exposure of patients in clinical trials. Moreover, molecular drug imaging studies could enable precision medicine by selecting the right drug at the right dose for the right patient and guide drug development to delivery behind the BBB with great promise for future therapy of CNS diseases.

DISCLOSURE

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